

RECOMMENDATIONS FOR

Aromatase inhibitors as adjuvant endocrine therapy

for post-menopausal women with hormone receptor-positive early breast cancer

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY THE NATIONAL BREAST CANCER CENTRE (NBCC)

This document supplements guideline recommendation 19 about the use of tamoxifen for the management of post-menopausal women with hormone receptor-positive early breast cancer contained in the NBCC *Clinical Practice Guidelines for the Management of Early Breast Cancer*, 2nd edition, 2001 (page 9).¹

PURPOSE

To provide statements and recommendations, based on the best available evidence, about the use of aromatase inhibitors as adjuvant endocrine therapy for post-menopausal women with hormone receptor-positive early invasive breast cancer.

BACKGROUND

Aromatase inhibitors are a class of endocrine drugs that are suitable for post-menopausal women with hormone receptor-positive breast cancer. They are ineffective in pre-menopausal women, including those rendered amenorrheic by chemotherapy who subsequently regain menstrual function.

Endorsed by:



EVIDENCE

This clinical practice guideline is based on available evidence from six randomised trials assessing three different ways of incorporating aromatase inhibitors in adjuvant endocrine therapy for hormone receptor-positive early breast cancer in post-menopausal women:

- starting adjuvant endocrine therapy with an aromatase inhibitor compared with starting with tamoxifen (ATAC, BIG-98)
- switching to an aromatase inhibitor after 2–3 years of tamoxifen compared with continuing on tamoxifen, both for total of 5 years of adjuvant endocrine therapy (IES, ITA, ABCSG/ARNO)
- extending adjuvant endocrine therapy by adding 5 years of an aromatase inhibitor after an initial 5 years of tamoxifen (MA.17).

(see table 1 on page 6 for details)

Adjuvant endocrine therapy with an aromatase inhibitor significantly improved disease-free survival in post-menopausal women with hormone receptor-positive early breast cancer compared with tamoxifen or placebo in all six available randomised trials. Improvements in overall survival have not been demonstrated but follow-up to date is relatively short. Most women had few side effects on either aromatase inhibitors or tamoxifen and, where reported, quality of life was comparable for aromatase inhibitors and tamoxifen. The long-term effects of aromatase inhibitors are not yet known. While some trials have examined the use of aromatase inhibitors for 5 years, the optimal duration of aromatase inhibitor therapy and the optimal sequence in which different adjuvant endocrine therapies should be administered for the management of early breast cancer is not yet established.

STATEMENTS AND RECOMMENDATIONS

Recommendations to an individual should be based on their risks without treatment, the benefits and harms of treatment, and their preferences. Recommendations should also take account of any uncertainties about long-term effects. In women at high risk of breast cancer recurrence, the known benefits of aromatase inhibitors are likely to outweigh their harms (both known and unknown). Conversely, in women at low risk of breast cancer recurrence, known or unknown harms of aromatase inhibitors could outweigh the known benefits. In women at intermediate risk of recurrence, the balance between benefits and harms is unclear.

Women at **high risk of recurrence** include those with involved lymph nodes, large primary tumours (>2cm) and high-grade tumours (grade 2–3). Women at **low risk of recurrence** include those with small, well-differentiated tumours and uninvolved lymph nodes. More extensive discussion of these issues can be found in the NBCC *Clinical Practice Guidelines for the Management of Early Breast Cancer*.¹

STATEMENTS**LEVEL OF TRIAL AND REFERENCE EVIDENCE**
(See Table 1 for details)

In post-menopausal women with hormone receptor-positive early breast cancer:

Starting adjuvant endocrine therapy with an aromatase inhibitor leads to fewer breast cancer recurrences than starting with tamoxifen	II	ATAC ² ; BIG 1-98 ³
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Switching to an aromatase inhibitor after 2–3 years of tamoxifen for a total of 5 years leads to fewer breast cancer recurrences than continuing with tamoxifen for 5 years	II	IES ⁴ ; ITA ⁵ ; ABCSG/ARNO ⁶
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Extending treatment with letrozole for 5 years leads to fewer breast cancer recurrences than observation without further treatment in women who have recently completed 5 years of adjuvant tamoxifen	II	MA.17 ⁷
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Treatment with an aromatase inhibitor leads to fewer contralateral breast cancers than treatment with tamoxifen or placebo	II	ATAC ² ; BIG 1-98 ³ ; IES ⁴ ; ITA ⁵ ABCSG/ARNO ⁶ ; MA.17 ⁷
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Arthralgia, loss of bone mineral density and fractures occur more frequently with aromatase inhibitors than with tamoxifen or placebo	II	ATAC ² ; BIG 1-98 ³ ; IES ⁴ ; MA.17 ⁷
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Venous thromboembolic events and endometrial cancer occur less frequently with aromatase inhibitors than with tamoxifen	II	ATAC ² ; BIG 1-98 ³
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Hot flushes, vaginal discharge and bleeding may occur less frequently and sexual dysfunction may occur more frequently with aromatase inhibitors than with tamoxifen	II	ATAC ² ; MA.17 ⁷
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The effects of aromatase inhibitors (compared with tamoxifen or placebo) on the risks of myocardial infarction and stroke are unclear and require results from trials with longer follow-up	II	ATAC ² ; BIG 1-98 ³ ; IES ⁴ ; MA.17 ⁷
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RECOMMENDATIONS**LEVEL OF EVIDENCE****AROMATASE INHIBITOR USED**

in trials on which recommendation is based

Adjuvant endocrine therapy is recommended for most women with hormone receptor-positive early breast cancer

Women should be informed of the potential side effects of the adjuvant endocrine therapy recommended to them, regardless of their risk of recurrence, and should be informed of any uncertainties about long-term effects

Women receiving adjuvant endocrine therapy should be reviewed regularly and monitored for side effects by clinicians familiar with these drugs

Reduction of bone mineral density in women receiving an aromatase inhibitor should be managed according to existing guidelines for women in general.⁸ This includes the identification and treatment of women at high risk of osteoporosis

I

For post-menopausal women with hormone receptor-positive early breast cancer who are at HIGH risk of breast cancer recurrence:

If the woman has not started adjuvant endocrine therapy, it is recommended that adjuvant endocrine therapy starts with an aromatase inhibitor (rather than tamoxifen)

II

Anastrozole, Letrozole

If the woman has been on adjuvant endocrine therapy with tamoxifen for 2–3 years it is recommended that therapy be switched to an aromatase inhibitor

II

Anastrozole, Exemestane

If the woman has been on adjuvant endocrine therapy with tamoxifen for 5 years it is recommended that adjuvant endocrine therapy be extended with Letrozole

II

Letrozole

RECOMMENDATIONS	LEVEL OF EVIDENCE	AROMATASE INHIBITOR USED
<p>For post-menopausal women with hormone receptor-positive early breast cancer who are at INTERMEDIATE risk of breast cancer recurrence:</p>		<p>in trials on which recommendation is based</p>
<p>Decisions about whether to use an aromatase inhibitor or tamoxifen should be based on an assessment of the risks and benefits of treatment for that individual</p>	II	
<p>For post-menopausal women with hormone receptor-positive early breast cancer who are at LOW risk of breast cancer recurrence:</p>		
<p>Adjuvant endocrine therapy with tamoxifen is recommended (rather than with an aromatase inhibitor) for most low-risk women as described in the NBCC <i>Clinical Practice Guidelines for the Management of Early Breast Cancer (2001)</i>¹ because the balance between long-term benefits and harms of aromatase inhibitors is presently unclear for such women</p>	II	
<p>For post-menopausal women with hormone receptor-positive early breast cancer who are intolerant of tamoxifen or who have a contra-indication to tamoxifen (regardless of risk of breast cancer recurrence):</p>		
<p>Adjuvant endocrine therapy with an aromatase inhibitor is recommended</p>	II	

SUMMARY OF RESULTS

Table 1: Trial details

TRIAL	FULL NAME	AROMATASE INHIBITOR	MEDIAN FOLLOW-UP	REFERENCE
ATAC	Arimidex, Tamoxifen Alone or in Combination	Anastrozole	68 months	2, 9-12
BIG 1-98	Breast International Group 1-98	Letrozole	26 months	3
IES	Intergroup Exemestane Study	Exemestane	31 months	4
ITA	Italian Tamoxifen Arimidex	Anastrozole	52 months	5
ABCSG/ARNO	Austrian Breast Cancer Study Group/Arimidex-Nolvadex	Anastrozole	26 months	6
MA.17	Late Letrozole Trial	Letrozole	28 months	7, 13, 14

DISEASE-FREE SURVIVAL

All trials showed statistically significant improvements in disease-free survival with *relative* risk reductions of about 15–40% for the use of aromatase inhibitors compared with tamoxifen either as initial therapy or after 2–3 years of tamoxifen; or around 46% for the use of an aromatase inhibitor compared with placebo after 5 years of tamoxifen. In general, similar improvements were seen in all components of disease-free survival – risk of local recurrence, distant recurrence or development of a contralateral primary tumour – although not every component of disease-free survival reached statistical significance on its own. With the short follow-up and the relatively good prognosis seen in most trials to date, absolute differences in disease-free survival are small (<4%) and *absolute* differences in *distant* disease-free survival are even smaller. However such differences would be expected to increase over time and to be larger in women with a poorer prognosis.

OVERALL SURVIVAL

No trial has shown a statistically significant improvement in overall survival for the whole group randomised to an aromatase inhibitor. Of the trials comparing an aromatase inhibitor with tamoxifen, the trial with the most mature follow-up (ATAC) shows no difference in overall survival, while the other trials show non-significant trends favouring the aromatase inhibitor compared with tamoxifen or placebo.² Reducing distant recurrences might be expected to translate into improved overall survival, but further follow-up is required to confirm this. Where an aromatase inhibitor was compared with placebo after 5 years of tamoxifen (MA.17), no overall survival benefit was seen in the group as a whole.⁷ However, a survival benefit was seen in the pre-specified subgroup with node-positive disease ($p=0.04$). Early reporting of the results and subsequent substantial crossover from placebo to aromatase inhibitor make it unlikely that a statistically significant survival difference will be seen in MA.17 overall.⁷

ADVERSE EVENTS

Aromatase inhibitors and tamoxifen were generally well tolerated in all six trials. Serious adverse events were rare and withdrawals due to adverse events were generally less frequent with aromatase inhibitors than with tamoxifen, and equally frequent with an aromatase inhibitor (letrozole) and placebo. Arthralgia, loss of bone mineral density and fractures were significantly more frequent with aromatase inhibitors compared with tamoxifen or placebo. Menopausal symptoms, venous thromboembolic events and endometrial cancer were significantly less frequent with aromatase inhibitors compared with tamoxifen. Longer follow-up is needed to determine whether differences in serum lipids and the small numbers of myocardial infarcts and strokes seen in these trials are attributable to aromatase inhibitors or tamoxifen or are merely due to chance.

QUALITY OF LIFE

Formal analyses of quality of life have been reported for two trials (ATAC and MA.17).^{2,7} Global assessments of quality of life were similar in women receiving anastrozole and tamoxifen in ATAC, and in women receiving letrozole and placebo in MA.17. Menopausal symptom scores were similar in women receiving anastrozole and tamoxifen in ATAC – scores in both arms worsened initially and then improved over time. There were no significant differences in overall quality of life or the aggregate of endocrine symptoms in this trial. Women receiving anastrozole reported more vaginal dryness, painful intercourse, and loss of sexual interest, but fewer cold sweats and vaginal discharge than women on receiving tamoxifen. In MA.17, letrozole was associated with slightly worse menopausal symptoms, sexual function, vitality, bodily pain, and physical function than placebo, but these differences affected only a small proportion of the women (6% or less).

STRENGTHS AND WEAKNESSES OF THE AVAILABLE EVIDENCE

The randomised trials discussed in this report are large, well designed, and well conducted. The short-term effects of aromatase inhibitors on disease-free survival in post-menopausal women with hormone receptor-positive early breast cancer are strong and consistent across a range of populations, agents and settings. Information about long-term effects on overall survival and adverse events is not yet available, and even with longer follow-up will be limited by unblinding and crossover in some trials. Clinical practice recommendations developed by the NBCC will be reviewed as additional significant evidence becomes available and revised as required.

UNRESOLVED HYPOTHESES RAISED BY THE CURRENT DATA

Whether particular subgroups of women with hormone receptor-positive early breast cancer might benefit more or less from the use of adjuvant endocrine therapy with an aromatase inhibitor compared with tamoxifen is of particular clinical relevance, but difficult to establish with any degree of certainty. For example, an exploratory analysis within ATAC suggested that the subset of women with oestrogen receptor-positive, progesterone receptor-negative breast cancers particularly benefited from the use of anastrozole. While there are plausible biological explanations for why this could be so, it is not a consistent finding across all trials (A.Howell, personal communication). This and other subgroup analyses (for example the effect of HER2 status) remain important questions for further research, but cannot be relied upon to inform current clinical practice.

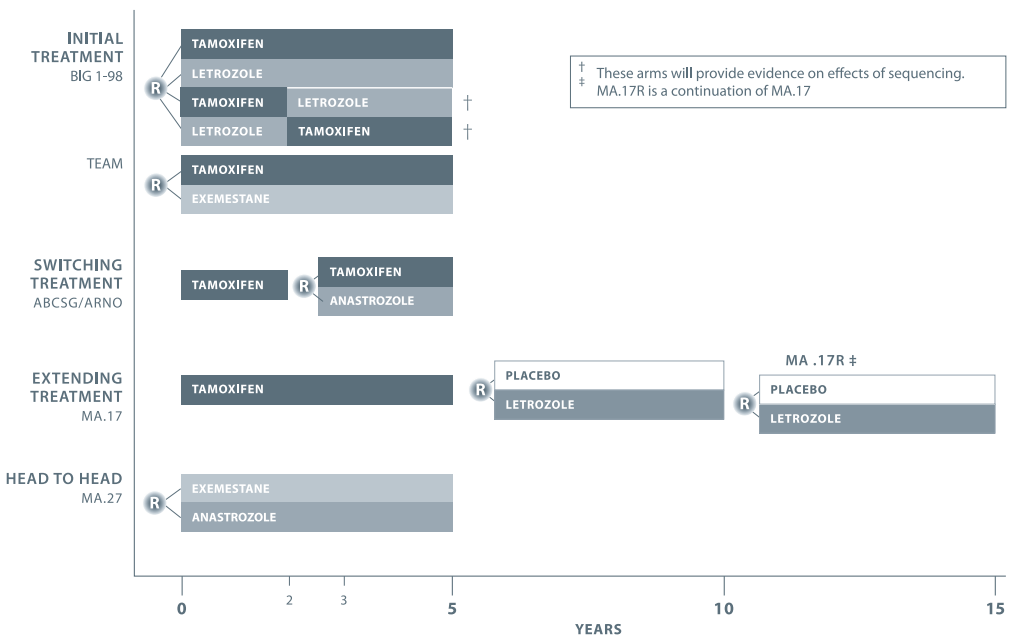
UNANSWERED QUESTIONS

Important unanswered questions about the use of aromatase inhibitors as adjuvant endocrine therapy for early breast cancer that are being addressed by ongoing trials include:

- the optimal duration of aromatase inhibitor therapy
- whether it is better to start adjuvant endocrine therapy with an aromatase inhibitor or to start with tamoxifen and switch to an aromatase inhibitor after 2–3 years, or vice versa
- the relative benefits and harms of different aromatase inhibitors
- the relative benefits and harms of aromatase inhibitors compared with tamoxifen in premenopausal women receiving ovarian suppression therapy, or in women rendered postmenopausal by chemotherapy
- the effects of aromatase inhibitors on cognitive function
- the management of bone mineral density reduction due to aromatase inhibitors.

The determination of menopausal status can be difficult, particularly in younger women who no longer have a uterus or who have become amenorrheic during chemotherapy.

ONGOING TRIALS ^{3,6,15-18}



REFERENCES

References included in systematic review to end May 2005

1. National Breast Cancer Centre. *Clinical practice guidelines for the management of early breast cancer (2nd Edition)*. Canberra: Commonwealth of Australia, 2001.
2. Howell A, Cuzick J, Baum M *et al*. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365(9453):60-2.
3. Thurlimann B. Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer: First results of IBCSG 18-98 / BIG 1-98. Paper presented at: Primary Therapy for Early Breast Cancer 9th International Conference, 2005; St Gallen, Switzerland.
4. Coombes RC, Hall E, Gibson LJ *et al*. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med*. 2004;350(11):1081-92.
5. Boccardo F. Switching to anastrozole (ANA) vs continued tamoxifen (TAM) treatment of early breast cancer (EBC). Updated results of the Italian tamoxifen anastrozole (ITA) trial. Paper presented at: 41st Annual Meeting of the American Society of Clinical Oncology (ASCO), 2005; Orlando, United States.
6. Jakesz R, Kaufmann M, Gnant M *et al*. Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial. Paper presented at: San Antonio Breast Cancer Symposium, 2004; San Antonio, TX, USA.
7. Goss PE, Ingle JN, Martino S *et al*. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;349(19):1793-802.
8. O'Neill S, MacLennan A, Bass S *et al*. Guidelines for the management of postmenopausal osteoporosis for GPs. *Aust Fam Phys* 2004;33(11):910-917.
9. Baum M, Budzar AU, Cuzick J *et al*. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359(9324):2131-9.
10. Baum M, Buzdar A, Cuzick J *et al*. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003;98(9):1802-10.
11. Fallowfield L, Cella D, Cuzick J *et al*. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol* 2004;22(21):4261-71.
12. Locker GY. Cost-utility analysis of anastrozole versus tamoxifen as primary adjuvant therapy in postmenopausal women in early breast cancer from a US healthcare system perspective: the 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial. Paper presented at: San Antonio Breast Cancer Symposium, 2004; San Antonio, TX, USA.
13. Karnon J, Johnston SRD, Delea TE *et al*. Cost-effectiveness of extended adjuvant letrozole after five years of tamoxifen in postmenopausal early breast cancer. *J Clin Oncol* 2004;22(14S):6044.
14. Whelan T, Goss PE, Ingle JN *et al*. Assessment of quality of life (QOL) in MA.17, a randomized placebo-controlled trial of letrozole in postmenopausal women following five years of tamoxifen. *J Clin Oncol* 2004;22(14S):517.

15. National Cancer Institute Clinical Trials PDQ. TEAM.
Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=69260&version=HealthProfessional&protocolsearchid=1501391> Accessed March 17, 2005.
16. National Cancer Institute Clinical Trials PDQ. NSABP B-33.
Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=68640&version=HealthProfessional&protocolsearchid=1501459> Accessed March 17, 2005.
17. National Cancer Institute of Canada. MA.17R.
Available at: http://www.ctg.queensu.ca/public/Clinical_Trials/public_ph_3_trial_summary.html#MA17R Accessed August 8, 2005.
18. National Cancer Institute Clinical Trials PDQ. MA.27.
Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=316325&version=HealthProfessional&protocolsearchid=1501386> Accessed March 17, 2005.

Articles containing information considered by the Working Group but published after May 2005

(Note: the following references do not represent a systematic review but are selected articles of relevance to this guideline)

Wasan KM, Goss PE, Pritchard PH *et al.* The influence of letrozole on serum lipid concentrations in postmenopausal women with primary breast cancer who have completed 5 years of adjuvant tamoxifen (NCIC CTG MA.17L). *Ann Oncol* 2005; 16: 707-715.

Boccardo F, Rubagotti A, Puntoni M *et al.* Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole trial. *J Clin Oncol* 2005; 23: 5138-5147.

Jakesz R, Jonat W, Gnant M *et al.* on behalf of the ABCSG and the GABG. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005; 366: 455-462.

Goss PE, Ingle JN, Martino S *et al.* Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; 97: 1262-1271.

Markopoulos C, Polychronis A, Zobolas V *et al.* The effect of exemestane on the lipidemic profile of postmenopausal early breast cancer patients: preliminary results of the TEAM Greek sub-study. *Breast Cancer Res Treat* 2005; 93: 61-66.

Whelan TJ, Goss PE, Ingle JN *et al.* Assessment of Quality of Life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. *J Clin Oncol* 2005; 23: 6931-6940.

Other articles of interest published subsequent to development of this guideline

Mann BS, Johnson JR, Kelly R *et al.* Letrozole in the extended adjuvant treatment of postmenopausal women with history of early-stage breast cancer who have completed 5 years of adjuvant tamoxifen. *Clin Cancer Res* 2005; 11: 5671-5677.

Dowsett M, Cuzick J, Wale C *et al.* Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: an hypothesis generating study. *J Clin Oncol* 2005; 23: 7512-7517.

National Prescribing Service Rational Assessment of Drugs and Research. Anastrozole (Arimidex) for the treatment of hormone-dependent early breast cancer in postmenopausal women. December 2005.

Membership of the NBCC Hormonal Therapies Guideline Working Group

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Pharmaceutical Benefits Scheme Indications for drugs mentioned in this guideline (as of July 2006). For updates after this date go to <http://www.health.gov.au/pbs/>

Tamoxifen:	Treatment of hormone-dependent breast cancer.
Anastrozole:	Treatment of hormone-dependent breast cancer in post-menopausal women. Not subsidised for primary prevention of breast cancer.
Letrozole:	Treatment of hormone-dependent advanced breast cancer in post-menopausal women. Not subsidised for primary prevention of breast cancer.
Exemestane:	Treatment of hormone-dependent advanced breast cancer in post-menopausal women with disease progression following treatment with tamoxifen citrate. Not subsidised for primary prevention of breast cancer.

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Full details of trial results are provided in the document *Aromatase Inhibitors as Adjuvant Therapy for Post-Menopausal Women with Hormone Receptor-Positive Early Breast Cancer: Evidence Summary* which can be accessed via the NBCC website at www.nbcc.org.au

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